Pure Appl. Chem., Vol. 80, No. 5, pp. 891–901, 2008.
doi:10.1351/pac200880050891

Catalytic enantioselective Reformatsky reactions*

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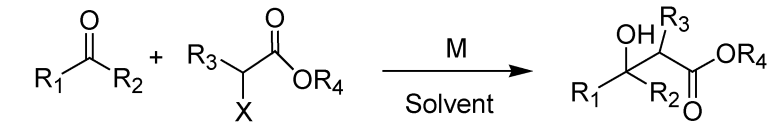
Abstract: The Reformatsky reaction is a venerable named reaction that was introduced more than 120 years ago. Diastereoselective variants based on the use of chiral auxiliary and enantioselective protocols, based on the employment of stoichiometric amount of chiral ligands, have been successfully applied in organic synthesis during the years. However, a facile and general catalytic enantioselective variant was still a difficult task. Recently, we have established a new general and straightforward methodology for catalytic enantioselective Reformatsky reaction based on different concepts. In this paper, we present our general finding in catalytic enantioselective Reformatsky reaction of ketones, imines, and aldehydes. Our simple methodologies could become benchmark reactions for testing new synthesized chiral ligands for asymmetric transformations.

Keywords: Reformatsky reaction; catalysis; enantioselective; aldehydes; imines; ketones.

The classical Reformatsky reaction was introduced in 1887 by Reformatsky [1] and consists of the zinc-induced formation of β-hydroxyalkanoates from the reaction of α-halocarbonyl compounds with aldehydes and ketones. Reformatsky reactions are now defined as those resulting from metal insertions into the carbon–halogen bond, which is activated by carbonyls or carbonyl-related groups in vicinal or vinylogous positions, with a variety of different electrophiles (Scheme 1).



X = Cl, Br, I
M = Sn, In, Zn, ...
Solvent = THF, Et_2O, CH_2Cl_2, ...

Scheme 1 Reformatsky reaction.

As the reaction is initiated by the insertion of zinc into the halogen–carbon bond, many studies were directed toward the activation of zinc, to facilitate its insertion [2], or by use of many different metals (Sm, Ti, Co, In) in low oxidation states. The major problem was the difference in the reactivity

*Paper based on a presentation at the 14th International Symposium on Organometallic Chemistry Directed Towards Organic Synthesis (OMCOS-14), 2–6 August 2007, Nara, Japan. Other presentations are published in this issue, pp. 807–1194.
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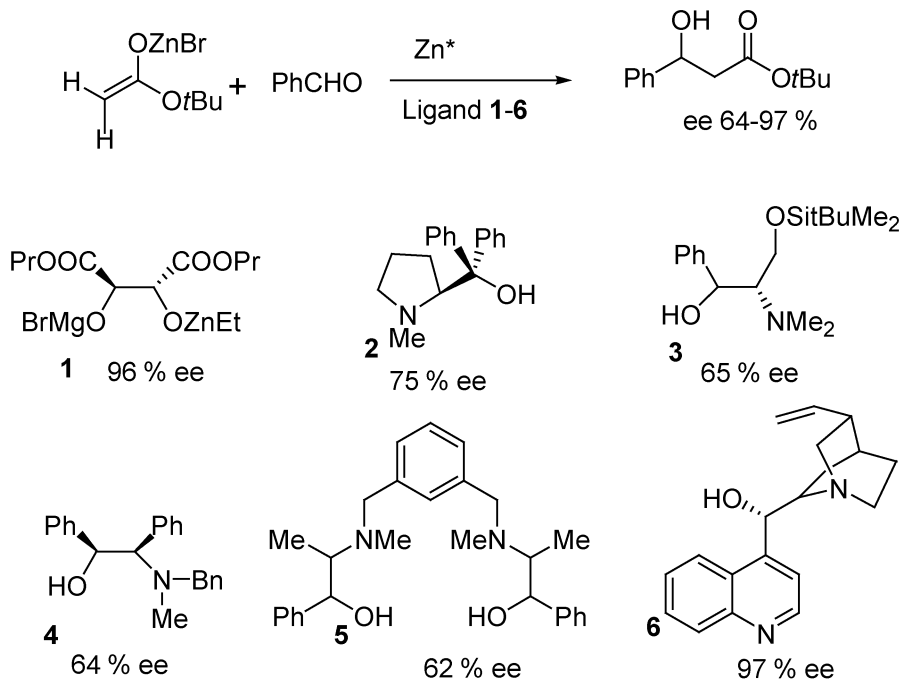
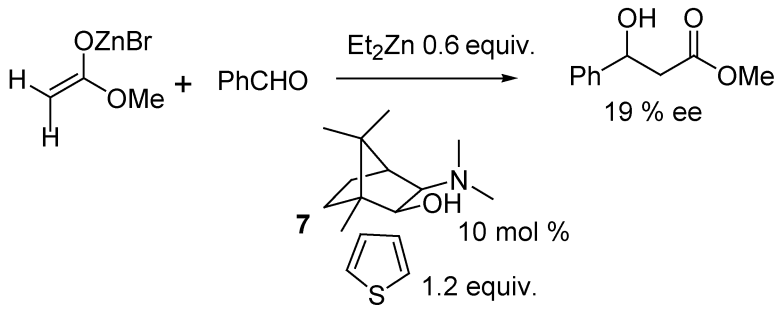
of different zinc sources. In fact, in the reaction with zinc, or with metal in a low oxidation state, the reaction is typically heterogeneous. Zinc is covered by zinc oxides, and reacts slowly with the halocompound. However, more efficient procedures and milder conditions have been developed with special forms of activated zinc such as Rieke-Zn [3], or Cu–Zn alloy [4]. Knochel has developed a straightforward and practical method for activating zinc [5], which is now commonly used to overcome problems in activation of zinc metal. The mild reaction conditions and the use of an inexpensive, nontoxic metal have made the development of stereoselective variants possible [6]. Many different ligands have been tested in an enantioselective variant of the Reformatsky reaction (Scheme 2).



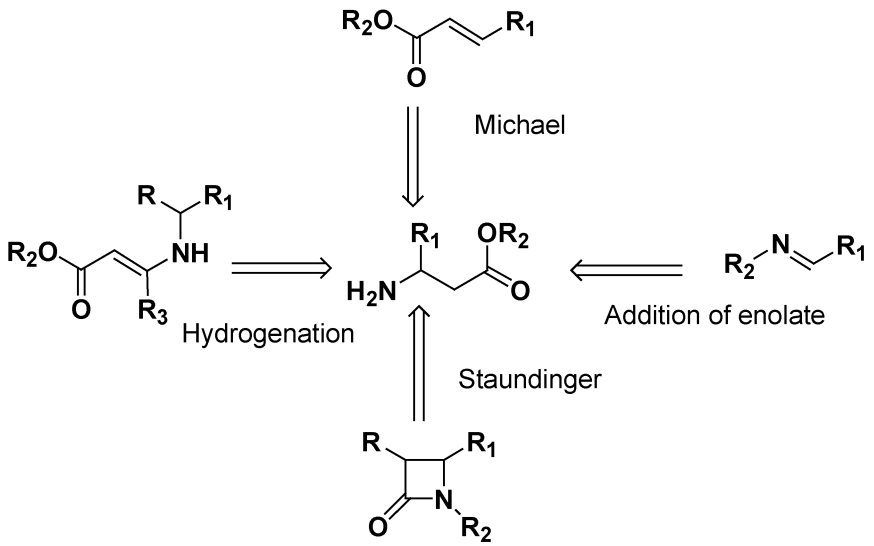
Scheme 2 Enantioselective Reformatsky reaction performed with stoichiometric amounts of the chiral ligands **1–6**.

Most of the ligands were used in more than stoichiometric amounts. In fact, the reactivity of the generated zinc enolate and the heterogeneous conditions have resulted in the quite difficult development of catalytic enantioselective variant, particularly with the use of chiral ligands, or promoters, in catalytic amounts. Knochel has recently developed a practical enantioselective variant of the Reformatsky reaction [7] carried out in the presence of the chiral ligand **7**, in which good levels of enantiomeric excess were reached with aliphatic, aromatic, and heterocyclic aldehydes, and where the use of different bromo esters was also considered. In the development of this version, a key issue seems to have been the addition of an equivalent of Et_2Zn to the reaction mixture. However, when the amount of **7**, employed in the model reaction, was reduced to 10 mol %, the enantiomeric excess went down considerably (Scheme 3).



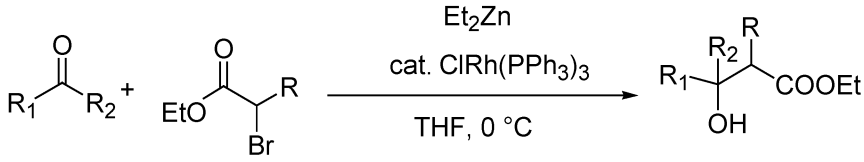
Scheme 3 Reformatsky reaction developed by Knochel with a catalytic amount of the chiral ligand **7**.

We become involved in the Reformatsky reaction in the design of new chiral Schiff bases formed with β-amino acids. A retrosynthetic analysis for the preparation of β-amino acids suggested an imino-Reformatsky reaction as a possible synthetic route (Scheme 4). However, in such a reaction the corresponding products are often isolated as a mixture consisting of β-aminoesters and β-lactams. A homogeneous variant of the Reformatsky reaction was employed in order to solve this problem.



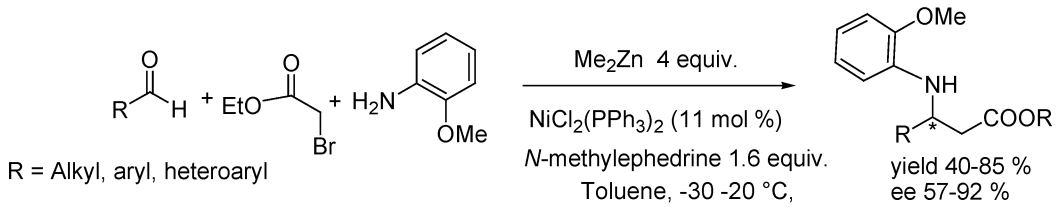
Scheme 4 Retrosynthetic analysis for the preparation of aminoesters.

Homogeneous reaction conditions enabled us to design a catalytic enantioselective transformation. In this context, homogeneous Reformatsky reactions based on the use of Me_2Zn or Et_2Zn have recently been reported (Scheme 5). Honda [8] suggested the use of Wilkinson's catalyst $Rh(PPh_3)_3Cl$, in the presence of Et_2Zn, which acts as a zinc source, while Adrian [9] discovered that a catalytic amount of the $Ni(PPh_3)_2Cl_2$ could effectively replace the more expensive Wilkinson's catalyst.



Scheme 5 Homogeneous version of the Reformatsky reaction developed by Honda.

Adrian also suggested the use of less nucleophilic Me_2Zn as a zinc source because it has less reactivity, compared to Et_2Zn, and produces no by-products derived from the transfer of a methyl group to the electrophiles. Adrian introduced another concept in his one-pot, three-component Reformatsky reaction with imines [9]. The classic Reformatsky reaction with imines presented the problem that a mixture of β-lactams and β-aminoesters was often isolated, because of the reaction conditions and imine partner. The use of a chelating imine, derived from *o*-methoxy aniline, was able to direct the Reformatsky reaction toward obtaining the β-amino ester. The *o*-methoxyaniline protecting group can be deprotected with an oxidative cleavage, and one of the newest reagents recently introduced was $PhI(OAc)_2$ [10]. The one-pot reaction conditions, coupled with a chelating imine, were key concepts for our first enantioselective one-pot, three-component Reformatsky reaction, carried out in the presence of an excess of *N*-methylephedrine as a chiral ligand [11]. Good enantiomeric excess (up to 92 %) and moderate yield were obtained, with the reaction showing a broad scope (Scheme 6).



Scheme 6 Enantioselective one-pot, three-component Reformatsky reaction.

It is worth noting the various tasks performed by Me_2Zn in these reactions: (a) Me_2Zn is the dehydrating agent responsible for the formation of the imine in situ; (b) Me_2Zn is able to reduce the Ni(II) salt to nickel(0); (c) Me_2Zn reacts with the incipient nickel enolate to form the reactive zinc enolate; and finally (d) Me_2Zn is able to coordinate *N*-methylephedrine, the amino alcohol used as a chiral ligand. A redox cycle can be suggested for the formation of the zinc enolate (Fig. 1).

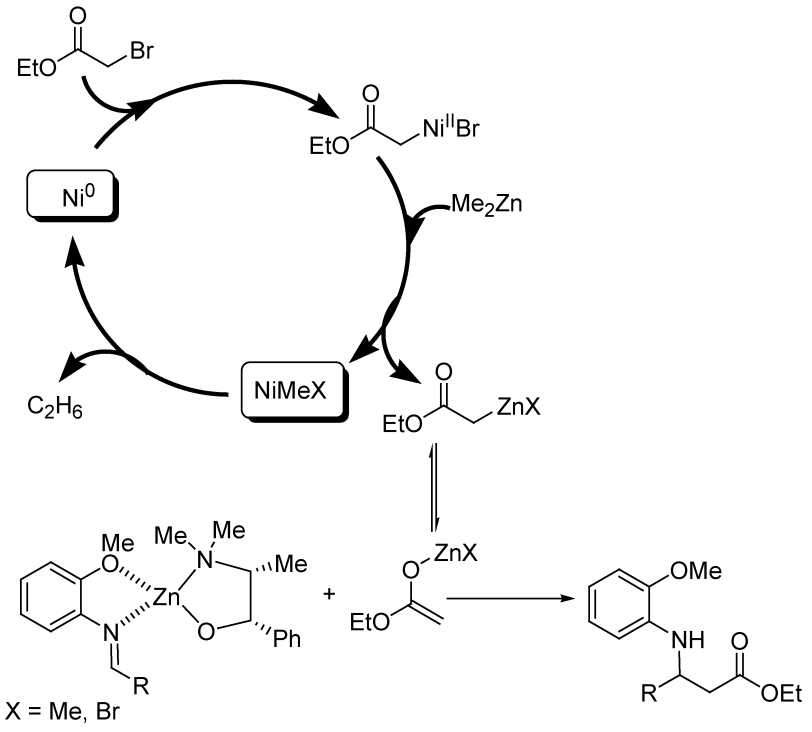
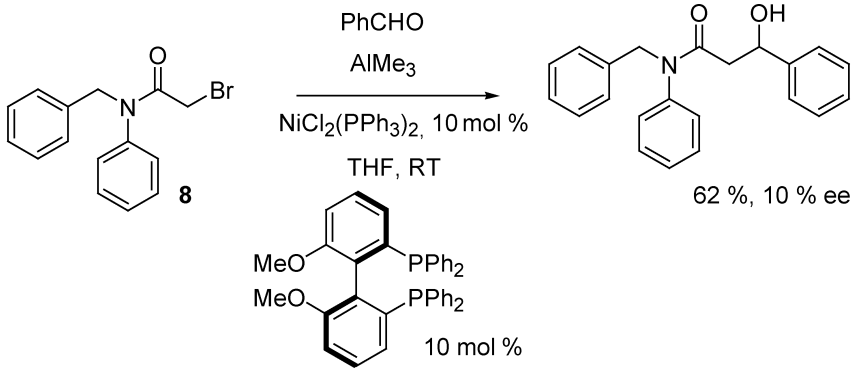


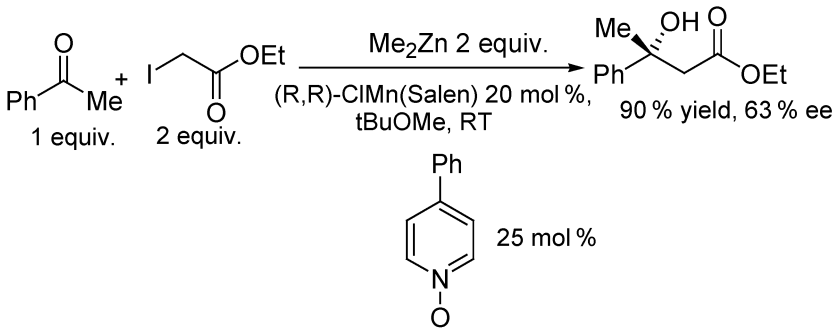
Fig. 1 Catalytic cycle for the enantioselective homogeneous one-pot, three-component imino-Reformatsky reaction.

A key feature of the cycle is the formation of metal enolate with low reactivity (Rh, Ni), unable to react with the imine. We immediately started a program directed toward the development of a catalytic version. In the homogeneous version of the Reformatsky reaction developed by Adrian, Honda, and us, the nickel complex is acting in the key step of the insertion in the halocarbonyl compound; therefore, we focused our attention toward the employment of a catalytic amount of nickel, in the presence of a suitable chiral ligand. Precedent work published by Fu [12] guided our investigation. The amide **8** was prepared and reacted with benzaldehyde in the presence of many different chiral ligands (Scheme 7) [13].



Scheme 7 Catalytic enantioselective Reformatsky reaction promoted by nickel and $AlMe_3$.

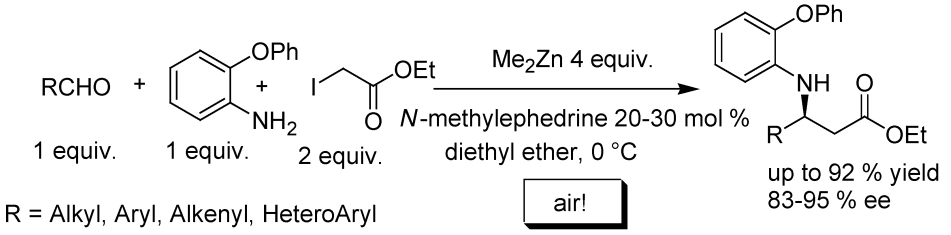
Unfortunately, in the best result obtained through the use of Roche's MeO–BiPHEP diphosphine as the chiral ligand [14], we recorded only 10 % of the enantiomeric excess. The reactivity of the zinc enolate was too high in order to allow the control of the reaction with chiral ligands, and probably, the nickel enolate formed in the initial step was rapidly transformed in the high reactive zinc enolate. In order to influence the formation of the zinc enolate, and controlling its concentration, we used another concept. The halogen–metal exchange is activated by ligands with high coordination numbers and capable of a strong donation [15]. In these transmetallations, the formation of ate transition states is responsible for the exchange reaction occurring between the two reagents. Moreover, the exchange of bimetallic reagents, prepared in the presence of inorganic salts, is determined by the saturation of the exchanged metal [16]. In fact, functionalized zinc reagents can be prepared by exchange reactions with Et_2Zn, or with the more reactive $i Pr_2Zn$ [17]; magnesium salts can strongly accelerate these reactions, and the formation of ate complex is involved in the accelerating effects. It is well known that zinc enolate can be prepared by the direct exchange of iodo esters with Et_2Zn [18] or $i Pr_2Zn$ [19]. Enantioselective Reformatsky variants, based on the exchange between iodoacetate and Et_2Zn, have also been developed [20]. The basic concept that we have applied in catalytic enantioselective Reformatsky reaction was to realize a controlled and mild formation of zinc enolate, using the less reactive Me_2Zn in the presence of a chiral zinc metal complex. Me_2Zn has lower reactivity, and even in the presence of chiral ligand its addition to aldehydes is not so straightforward [21]. We thought that a homogeneous version of the Reformatsky reaction, coupled with a system able to accelerate the exchange between iodoacetate and Me_2Zn, and controlling the formation of the reactive enolate, would be effective in a catalytic Reformatsky reaction. Many different ligands were tested, performing the model reaction in the presence of benzaldehyde and acetophenone. In general, no reaction occurs, even in the presence of amino alcohols. Among all ligands tested, we discovered that the exchange reaction was catalyzed by salen ligands. Although is still unclear how (see infra), the salen ligand was able to accelerate this exchange; probably the Lewis basic–acid nature of the metal salen complexes played a decisive role [22]. Different salen complexes were tested, and among them ClMn(salen) (Scheme 8) emerged as the most effective catalyst, in the reaction with benzaldehyde. Studying the corresponding reaction with acetophenone gave a higher value of enantiomeric excess; therefore, this model reaction was systematically studied. Different ClMn(salen) complexes were also synthesized and tested, with scarce results.



Scheme 8 Catalytic enantioselective Reformatsky reaction promoted by ClMn(salen) complex.

The reaction conditions were varied in the case of different ketones, and the additive 4-phenylpyridine-*N*-oxide was found to be important, performing the reaction in *t*BuOMe [23]. Highly diluted conditions and 20 mol % of ClMn(salen) were necessary in order to guarantee higher enantioselectivity in the reactions. In these conditions, the reaction is quite sluggish, and several days were necessary in order to reach a good conversion. Moreover, the ClMn(salen) appears unstable toward the selected

reaction conditions, and a slow but progressive transformation of ClMn(salen) in Zn(salen), due to the presence of excess of Me_2Zn, took place. The reaction conditions were tested with the one-pot, three-component imino Reformatsky reaction, without a great success. However, *N*-methylephedrine, in conjunction with the use of ethyl iodoacetate, was found to be the effective chiral ligand. In order to promote the reaction using a catalytic amount of *N*-methylephedrine, a systematic investigation of the reaction parameters was undertaken, and during these investigations, it was clear that the transmetallation between iodoacetate and Me_2Zn was sometimes accelerated. Many reaction conditions were investigated, but somehow, the key point was missing. The results seem to have been not reproducible. Finally, it was clear that adventitious traces of air were ultimately responsible for the effective transmetallation. Consequently, air was introduced into the reaction flask though a dry-tube, and good yield and excellent enantioselectivity were obtained in the one-pot, three-component imino-Reformatsky reaction with aromatic, aliphatic, and heteroaromatic aldehydes (Scheme 9) [24].



Scheme 9 Catalytic enantioselective one-pot, three-component imino Reformatsky reaction promoted by air.

The activation of Me_2Zn seems to be possible using this quite different concept. It is well known that Me_2Zn in the presence of oxygen generates alkyl peroxides (ZnOOR), which are able to initiate radical reactions [25]. Zinc enolate can be generated via a radical mechanism (Fig. 2), and the catalytic enantioselective addition of these enolates to imines can then be carried out for the first time. There are

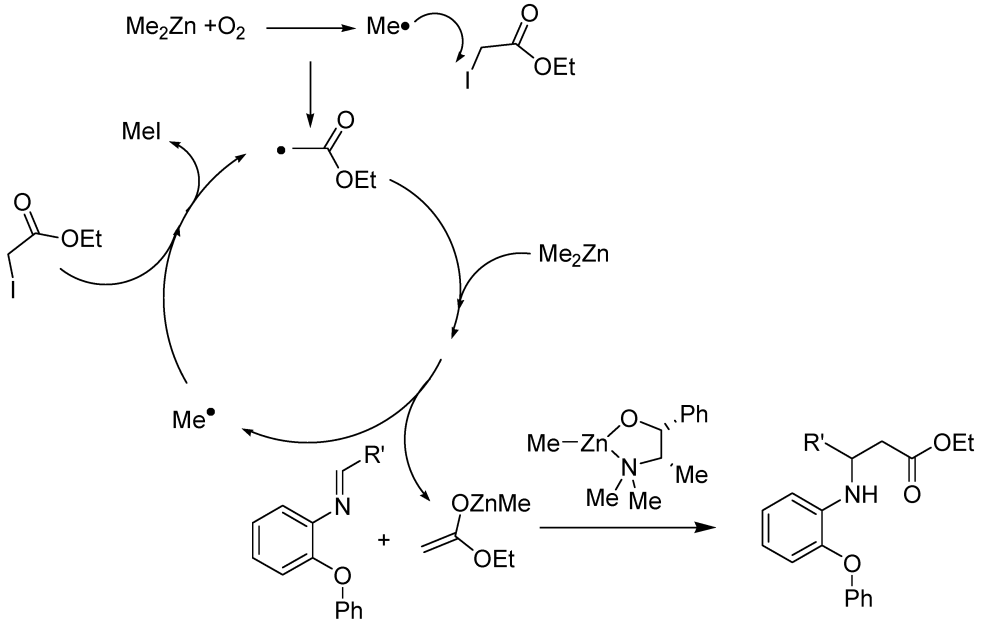
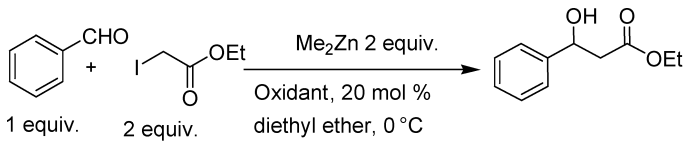


Fig. 2 Catalytic cycle for the enantioselective Reformatsky reaction promoted by air.

some literature precedents for the generation of enolate mediated by the radical process described by Oshima [26]. Similarly, Et_3B has been used as a radical initiator, and Danishefsky has found that boron enolate can easily be prepared by exchange reaction at a low temperature with an iododerivative in a boron Reformatsky process [27]. Finally, it is worth mentioning that Tomioka has used Me_2Zn for promoting radical reactions [28].

This way of generating zinc enolate is also suitable for a catalytic enantioselective Reformatsky reaction with aldehydes, using the appropriate amino alcohol. We started the detailed investigation of a new catalytic Reformatsky reaction with aldehydes studying different amino alcohols and performing the reaction in concentrate conditions, *N*-pyrrolidinylephedrine was found to be the best ligand for this transformation, and the reaction conditions were varied accordingly [29]. In particular, slow addition of the reagents was investigated, showing that the diluted conditions were essential for reaching good stereoselectivity, then a mixture of solvents (diethyl ether and THF) in 0.03–0.04 M concentration were used. In these conditions, we reached good enantiomeric excess in the model reaction with benzaldehyde, operating at 0 °C. The generation of the enolate seems mediated by a radical cycle, in which a promoter is necessary. Several types of oxidants, operating via the single-electron tunneling (SET) mechanism or via direct oxidation, are able to generate radical species and, therefore, were also investigated. The model reaction with benzaldehyde, in the absence of chiral ligand, was carried out with different oxidants, used in 20 mol %; Table 1 reports the results obtained. Different oxidants used in the catalytic amounts of 20 mol % are suitable to induce the formation of radicals and to promote the formation of the zinc enolate in the homogeneous reaction conditions [29].

Table 1 Reaction of benzaldehyde with iodoacetate and Me_2Zn promoted by oxidants.

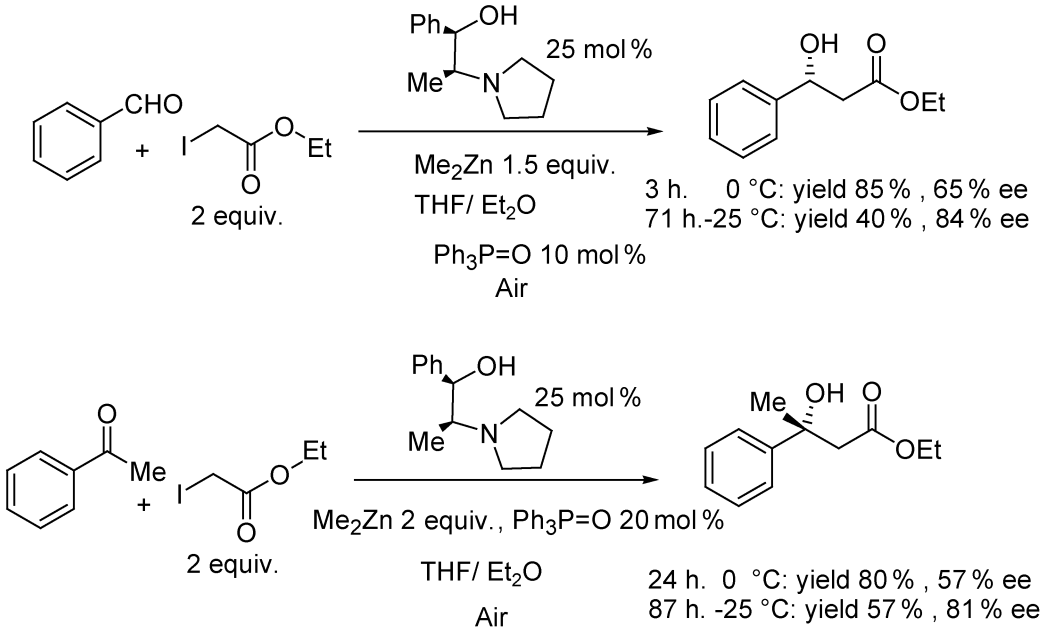


Entry	Oxidant[a]	Yield[b]
1	air	88
2	H_2O_2 urea	73
3	*t*BuOOH	91
4	DDQ	20
5	$FeCp_2^+$	89
6	Oxone	40
7	$PhI(OAc)_2$	61
8	PhI=O	33
9	CAN	85

[a]All the reactions were carried out in Et_2O at 0 °C and were quenched after 4 h. The oxidant was used in 20 mol %, except in entry 1, where air was allowed to enter the reaction flask by a drying tube.
[b]Isolated yield of product purified by chromatography.

These results were optimized with different aldehydes, using two different protocols in the function of the type of substrates employed in the reaction. From the results obtained, air was considered the least expensive and available oxidant for promoting the reaction. In the case of non-enolizable aldehydes, using Ph_3P=O in 30 mol % as additive added to the preformed enolate (generated by introduction of air to the reaction flask containing Me_2Zn and ethyl iodoacetate), we have obtained in 1–2 h excellent yields for almost all types of aromatic aldehydes tested. For enolizable aldehydes, the rapid and successive addition of all of the reagents in the reaction flask gave excellent yields [29]. This protocol

was applicable also to ketone, and to halo ketones, substrates highly susceptible under basic conditions, and toward basic enolates. The enantioselective variant of the reaction is still under investigation, but preliminary results obtained with benzaldehyde and acetophenone (Scheme 10) are quite promising [29].



Scheme 10 Catalytic enantioselective Reformatsky reaction with benzaldehyde and acetophenone.

Although a detailed mechanistic investigation is necessary in order to conclude that radical species are involved in these catalytic reactions, recently published results are connecting quite diverse protocols that we have discovered. Van Koten reported some years ago that complexes of alkylzinc are able to undergo SET reactions liberating radicals [30]. It is quite remarkable that when we studied the generation of the zinc enolate in the presence of chiral ligands or metal complexes, only salen (performing the reaction under strictly anaerobic conditions) or salen metal complexes were able to activate iodoacetate toward the transmetallation with Me_2Zn. Recent results reported by Stack point out that SET reaction in the presence of salen ligand are able to form radical species [31]. The generation of the radical promoted transmetallation of iodoacetate with Me_2Zn with air or via salen are in some way related and are showing that there are open possibilities for designing a successful catalytic cycle for generating enolate with different metal precursors and alkyl reagents. The fine-tuning of these processes may give the possibility to explore new chemistry and new reactions, allowing the formation of the challenging quaternary stereogenic centers in a controlled and simple way. These and other options are under active investigation in our laboratory, and we hope to open a new venue to the old but still respectable Reformatsky reaction.

ACKNOWLEDGMENTS

PGC expresses eternal gratitude to his former and current coworkers, and acknowledges the generous funding of Johnson Matthey, STMicroelectronics, and Ciba. PGC is grateful to UE and the Royal Society of Chemistry for support and for giving him the opportunity to establish effective collaborations

with outstanding scientists all over the world. Finally, Bologna University and MIUR are acknowledged for financial support of the research over the past 14 years.

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